PATENT COOPERATION TREATY 09/701583

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
991058woMekk		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/04013	10/06/1999	10/06/1998
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE .. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/12/1999	18.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pilling, S Telephone No. +49 89 2399 8461

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/04013

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-15 as originally filed

Claims, No.:

1-13 as originally filed

Drawings, sheets:

1/11-11/11 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 12,13.

because:

☒ the said international application, or the said claims Nos. 12,13 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,9-11
	No:	Claims	1-4,6-8,12,13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-11 (for claims 12 and 13 see the comments under "ITEM III" on separate sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 12 and 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

2. In agreement with the findings of the International Searching Authority, it is considered that there is lack of unity of invention (Rule 13.1 PCT) in respect of the present claims. In this regard, there is no clear technical relationship involving one or more of the same or corresponding special technical features (Rule 13.2 PCT) linking the different oligonucleotide sequences of present Claim 10. Hence, as far as can presently be determined each of these oligonucleotide sequences presently appears to form a separate invention. In view of the large number of further inventions, and the possibility that some of these sequences could potentially be linked by a possible common inventive concept (see the further comments relating to lack of unity of invention herein below) the Applicant is advised that the following examination has been carried out in respect of all claims and parts thereof. It seems likely, however, that objection to lack of unity of invention will be raised at a later stage.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. The present application relates to medicaments comprising (i) an inhibitor of TGF-β or TGF-β- receptors, VEGF or VEGF receptors, interleukin-10 or interleukin-10 receptors, PGE-2 or PGE-2 receptors and (ii) a stimulator positively effecting an immune response (Claims 1 to 9), methods of treating neoplasms or infectious diseases therewith (Claims 12 and 13) and certain oligonucleotides *per*

se (Claims 10 and 11).

4. Claims 12 and 13 relate to methods of treatment of the human or animal body by therapy. In this regard, for the assessment of these claims with respect to industrial applicability, no unified criteria exist in the PCT. Furthermore, patentability can be dependent on the formulation of the claims. The EPO, for example does not recognize as industrially applicable, the subject matter of claims directed to a method of treatment of the human or animal body or to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D6 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

Claims 1 to 9, 12 and 13; medicaments and methods of treatment therewith

6. Document D1 (WO-A-96/02143) discloses compositions comprising cells which have been genetically modified to inhibit the expression of an immunosuppressive agent and to secrete an immunostimulatory agent. Inhibition of the immunosuppressive agent may be via genetic modification of the cell to express an antisense nucleic acid directed against an immunosuppressive isoform of TGF-β or a single chain antibody directed against the immunosuppressive agent. The cell may also be genetically modified to express an immunostimulatory agent such as a cytokine, *e.g.* IL-4 or GM-CSF. The cells of document D1 are said to function as antitumour vaccines and are therefore considered to be medicaments within the definition of present Claim 1.

7. Document D1 goes on to describe experimental treatment of tumour bearing rats with cells genetically modified to express antisense TGF-β2 and IL-2. Thus, in the latter case, the cells comprise an "*inhibitor of the effect of a substance negatively affecting an immune response*" (*cf* the wording of present Claim 1), *i.e.* this could be taken as being either the DNA which encodes the antisense nucleic acid directed against an immunosuppressive isoform of TGF-β or the antisense nucleic

acid produced thereby. The cells of document D1 further comprise "*at least one stimulator positively affecting an immune response*" (*cf* the wording of present Claim 1), *i.e.* this could be taken as being the DNA encoding the IL-2 *or* the IL-2 produced thereby.

8. Thus, the subject matter of Claims 1 to 4, 6 to 8, 12 and 13 is not new in view of the disclosure of document D1 (Article 33(2) PCT).

9. With reference to the above comments concerning lack of novelty of Claims 1 to 4, 6 to 8, 12 and 13, it is further noted that the present application does not describe a medicament in which the inhibitor and stimulator are present as constituents of modified whole tumour cells. Nevertheless, the claims which, express the invention in more general terms, do not seem to exclude the latter possibility. Hence, it is considered that the invention as presently claimed is not clearly distinguished from the prior art as disclosed in document D1.

10. With reference to the above comments concerning lack of novelty of Claims 1 to 4, 6 to 8, 12 and 13 it is also noted that any conflict between the disclosure of document D1 and further publications by the same author (*i.e.* Proc. Nat. Acad. Sci., 93, (1996), 2909-2914) would only seem to be potentially relevant to an objection to lack of inventive step based on document D1 and would be unlikely to have any bearing on lack of novelty.

11. None of the documents appears to disclose a medicament according to Claim 5 or Claim 9. Thus, the subject matter of these claims is new (Article 33(2) PCT).

12. Nevertheless, the subject matter defined by dependant Claims 5 and 9 comprises no technical feature(s) which would result in an inventive technical effect, Thus the latter claims are considered to lack inventive step in view of the disclosure of document D1 and fail to meet the requirements of Articles 33(3) PCT.

13. It is further noted, for the sake of completeness, that document D6 (Akporiaye *et al*) teaches that modifying tumour cells to express both antisense TGF-β and interferon-γ renders them more immunogenic. This document appears to teach directly towards the simultaneous modification of tumour cells *in vivo* using an

antisense TGF-β gene, *i.e.* an "*inhibitor of the effect of a substance negatively affecting an immune response*" (*cf* the wording of present Claim 1) and an IFN-γ gene, *i.e.* "*at least one stimulator positively affecting an immune response*" (*cf* the wording of present Claim 1). Hence, this document is considered to make therapy of tumour cells with a medicament comprising an anti-sense TGF-β and interferon-γ encoding DNA obvious. Consequently, in the event that present Claims 1 to 13 are amended to make them novel and inventive over document D1, then it appears likely that such amended claims would be obvious in view of the disclosure of document D6 (Article 33(3) PCT).

Claims 10 and 11; oligonucleotides *per se*

14. None of the documents cited in the search report appear to disclose any of the specific oligonucleotide sequences according to Claim 10. Thus, the subject matter of Claims 10 and 11 is new (Article 33(2) PCT).

15. The following comments are relevant to lack of inventive step of Claims 10 and 11; each of documents D1 to D6 show that antisense oligonucleotides directed against isoforms of TGF-β at least are known. Hence, there seems to be invention in merely providing new antisense sequences without any surprising properties. In this regard, the comments regarding surprising cross inhibition of different isoforms of TGF-β by certain of the present sequences have been noted (see page 6 line 20 to page 7 line 17). Nevertheless, it is considered that these advantages would not apply to all of the presently claimed sequences, particularly not to antisense sequences directed against non-TGF-β targets such as VEGF (see SEQ ID No. 119-155 and 165), flt (see SEQ ID No. 156, 157 and 166) or MCP-1 (see SEQ ID No. 159-164). Any surprising technical effect relied upon to demonstrate inventive step for the sequences of Claim 10 must be shown to be valid for each of the sequences claimed therein.

16. It is also noted that as advised in the ISR (see also item IV herein above), each of the sequences of Claim 10 presently appears to relate to a separate invention. In order to show that the sequences thereof relate to a single invention, the same surprising technical effect must be valid for each of the sequences claimed therein. In the event that different technical effects are advanced for different

groups of sequences, then it would be considered that such different groups of sequences would clearly relate to separate inventions.

Re Item VII
Certain defects in the international application

17. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII
Certain observations on the international application

18. The term "*stimulator positively effecting an immune response*" used in Claim 1 is vague and unclear (Article 6 PCT). Similarly, many of the further definitions of said "*stimulator*" in Claim 8 are also unclear. In this regard, it is further noted that certain substances, *e.g.* penicillin, may evoke or "*positively effect*" an immune response in certain hypersensitive individuals but not in other individuals. Hence, the definition of said stimulator depends in part on the patient and is indeterminate in the context of a claim to a composition *per se*.

19. Further to the above comments it is noted that the present experiments only appear to show that cytokine stimulators, *i.e.* GM-CSF or IL-4, would be likely to have a beneficial therapeutic effect. The generalisation of these examples to include for example, "*retroviruses*" [see page 3(b)] does not appear to be credible or supported by said experimental evidence. Hence, the term "*stimulator positively effecting an immune response*" is considered to be unduly broad and speculative (Article 6 PCT).

20. The further definitions of the "*inhibitor*" and "*stimulator*" in Claims 2 and 7 appear redundant in view of the previous definition of these substances in Claim 1. Hence Claims 2 and 7 lack conciseness and result in overall lack of clarity of the scope of the claims (Article 6 PCT)

21. Claim 11 appears to be incomplete

22. Claim 5 is ultimately appendant to Claim 1 and indicates that the inhibitor may be an oligonucleotide according to Figure 1. Figure 1, however, includes oligonucleotides inconsistent with the definition of the inhibitor of Claim 1, *e.g.* SEQ ID 161 which is directed against MCP-1. Hence, the subject matter of Claim 5 seems inconsistent with that of Claim 1 (see also page 6 lines 1 to 4).

23. Claim 13 formally appears appendant to Claim 12 but includes treatment of "*hyperproliferative diseases*". Treatment of this category of diseases appears to be broader in scope than the treatment of "*neoplasm or infectious diseases*" according to Claim 12. Hence Claim 13 is incorrectly appendant to Claim 12.

PATENT COOPERATION TREATY

09/701583

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

MEYERS, Hans-Wilhelm
Postfach 10 22 41
D-50462 Köln
ALLEMAGNE

WK	Sg	W	Da	Hi	HPJ	ME	TW	JH	K

21. SEP. 1999

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
03 September 1999 (03.09.99)	
Applicant's or agent's file reference	**International application No.**
991058woMekk	PCT/EP99/04013

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH (for all designated States except US)
SCHLINGENSIEPEN, Karl-Hermann et al (for US)

International filing date	:	10 June 1999 (10.06.99)
Priority date(s) claimed	:	10 June 1998 (10.06.98) 25 July 1998 (25.07.98)
Date of receipt of the record copy by the International Bureau	:	26 July 1999 (26.07.99)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,US,UZ,VN,YU,ZA,ZW

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

G. Bähr

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
03 September 1999 (03.09.99)	
Applicant's or agent's file reference	**International application No.**
991058woMekk	PCT/EP99/04013

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] confirmation of precautionary designations
- [X] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

WO 99/63975
PCT/EP99/04013

PATENT COOPERATION TREATY

09/701583

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
MEYERS, Hans-Wilhelm
Postfach 10 22 41
D-50462 Köln
ALLEMAGNE

Date of mailing (day/month/year) 16 December 1999 (16.12.99)	
Applicant's or agent's file reference 991058woMekk	**IMPORTANT NOTICE**
International application No. PCT/EP99/04013	**International filing date** (day/month/year) 10 June 1999 (10.06.99)
Priority date (day/month/year) 10 June 1998 (10.06.98)	
Applicant BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   16 December 1999 (16.12.99) under No. WO 99/63975

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra
Telephone No. (41-22) 338.83.38

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 48/00, 31/70, 38/20, 38/19, C12N 15/11 //
(A61K 38/20, 31:70) (A61K 38/19, 31:70)

A3

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(30) Priority Data:

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Published
With international search report.

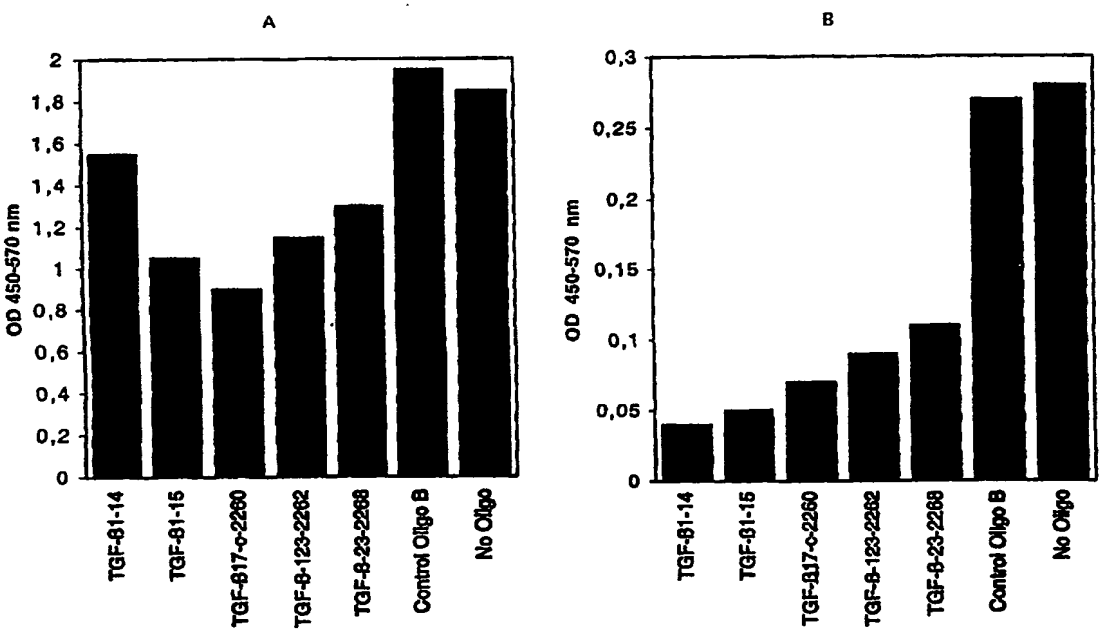
(88) Date of publication of the international search report:
3 August 2000 (03.08.00)

(71) Applicant *(for all designated States except US)*: BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH [DE/DE]; Gerhard–Gerdes–Strasse 19, D–37079 Göttingen (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SCHLINGENSIEPEN, Karl–Hermann [DE/DE]; Pappelweg 3, D–37085 Göttingen (DE). SCHLINGENSIEPEN, Reimar [DE/DE]; Am Goldgraben 13, D–37073 Göttingen (DE). BRYSCH, Wolfgang [DE/DE]; Calsowstrasse 56, D–37085 Göttingen (DE).

(74) Agent: MEYERS, Hans–Wilhelm; Postfach 10 22 41, D–50462 Köln (DE).

(54) Title: A METHOD FOR STIMULATING THE IMMUNE SYSTEM



(57) Abstract

Medicament comprising a combination of at least one inhibitor of the effect of a substance negatively effecting an immune response, the substance selected from the group consisting of TGF–β and its receptors, VEGF and its receptors, interleukin 10 (IL–10) and its receptors, PGE_2 and its receptors, wherein the inhibitor has a molecular weight of less than 100 kDa and at least one stimulator positively effecting an immune response.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04013

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K48/00 A61K31/70 A61K38/20 A61K38/19 C12N15/11
//(A61K38/20,31:70),(A61K38/19,31:70)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61P A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 02143 A (SIDNEY KIMMEL CANCER CENTER) 1 February 1996 (1996-02-01) page 4, line 16 -page 4, line 32 page 11, line 30 -page 12, line 1 page 12, line 22 -page 12, line 28 page 16, line 29 -page 17, line 9 example II ---	1-13
X	WO 94 25588 A (BIOGNOSTIK GES ;SCHLINGENSIEPEN GEORG FERDINAN (DE); BRYSCH WOLFGA) 10 November 1994 (1994-11-10) claim 1 --- -/--	10,11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2000	17. 05.00

Name and mailing address of the ISA	Authorized officer
European Patent Office. P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Pilling, S

11

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04013

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JACHIMCZAK P ET AL: "The effect of transforming growth factor-beta 2-specific phosphorothioate-anti-sense oligodeoxynucleotides in reversing cellular immunosuppression in malignant glioma." JOURNAL OF NEUROSURGERY, vol. 78, no. 6, June 1993 (1993-06), pages 944-951, XP000886109 final paragraph of the "Materials and methods" on page 946 "discussion" on page 948 ---	10,11
X	SPEARMAN M ET AL: "Antisense oligodeoxyribonucleotide inhibition of TGF - beta 1 gene expression and alterations in the growth and malignant properties of mouse fibrosarcoma cells." GENE, vol. 149, no. 1, 4 November 1994 (1994-11-04), pages 25-9, XP002089439 abstract; table 1 ---	10,11
X	WO 95 00103 A (CHUNG HUN TAEG ;IL YANG PHARM CO LTD (KR)) 5 January 1995 (1995-01-05) claim 5 ---	10,11
X	AKPORIAYE ET AL: "Concomitant expression of interferon-gamma and antisense TGF-beta transgenes enhances the immunogenicity of a murine mammary carcinoma" CANCER GENE THERAPY vol. 4, no. 6 conf. suppl. S55 6th International Conference on Gene Therapy of Cancer, San Diego, California, USA, Nov 20-22, 1997 XP000886176 abstract -----	1-13

11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/04013

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-9,12-13 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-9,12-13 (part)

Present Claim 1 relates to a medicament comprising a combination of;

i) an inhibitor of TGF-beta or TGF-beta receptors, VEGF or VEGF receptors, interleukin-10 or interleukin-10 receptors, PGE-2 or PGE-2 receptors and,

ii) a stimulator positively effecting an immune response

Each of these broad functionally defined categories of compounds (i) and (ii) includes many thousands of possible medicaments with the result that present Claim 1 comprises many, possible permutations. Furthermore, the Applicant is advised that, in general, compounds cannot be sufficiently defined by their function to the extent that a full search can be carried out.

Moreover, the definition of the "stimulator positively affecting the immune response" is vague and unclear.

Hence, in view of the above considerations a search of the full breadth of the present Claims 1 to 9 and 12 to 13 is impossible. Consequently, the search has been directed, in so far as practically feasible, to the general idea underlying the present invention and those combinations of medicaments which are most clearly described and exemplified namely combinations of;

i) an antisense oligonucleotide directed against TGF-beta or TGF-beta receptors, VEGF or VEGF receptors, interleukin-10 or interleukin receptors, PGE-2 or PGE-2 receptors, particularly the oligonucleotides of Claim 10 and;

ii) a stimulator selected from GM-CSF, SCF, CSF, IFN-gamma, FLT-3, MCP-1, IL-2, IL-4, IL-12, IL-18 (see page 3 lines 3 to 6); the stimulators described in categories (a), (b), (c) on present page 3; ras protein, p53 protein, EGF-receptor protein, retinoblastoma protein and derivatives thereof (see category (l) on present page 4).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 to 9, 12 and 13

Medicament comprising

i) an inhibitor of TGF-beta or TGF-beta receptors, VEGF or VEGF receptors, interleukin-10 or interluekin receptors, PGE-2 or PGE-2 receptors in combination with;

ii) a stimulator positively effecting an immune response

2. Claims: 10,11 (part)

An oligonucleotide having the sequence No. 55

3. Claims: 10,11 (part)

An oligonucleotide having the sequence No. 56

Each of the further sequences 57 to 213 relates to a further separate invention. Hence, inventions 4 to 158 are as defined herein above for invention 3. wherein oligonucleotide sequence No. 56 is replaced in turn by each of sequence No.'s 57 to 213.

i.e the present application comprises 160 inventions in total

With reference to the above identified inventions, it is noted that antisense oligonucleotides against TGF-beta at least are known (see each of the documents cited in the accompanying search report). Hence, there is no novel common inventive concept or idea linking the production of further anti-sense oligonucleotides as defined in Claims 10 and 11 which are directed against diverse targets such as TGF-beta, VEGF, flt, flkl and MCP-1.

Since all searchable claims could be searched without excessive additional effort justifying an additional fee, the present search report relates to ALL INVENTIONS IDENTIFIED ABOVE.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/EP 99/04013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9602143 A	01-02-1996	US 5772995 A	30-06-1998
		AU 711730 B	21-10-1999
		AU 3217895 A	16-02-1996
		CA 2195334 A	01-02-1996
		EP 0771147 A	07-05-1997
WO 9425588 A	10-11-1994	AU 6794594 A	21-11-1994
		EP 0695354 A	07-02-1996
		JP 8509370 T	08-10-1996
WO 9500103 A	05-01-1995	KR 9705347 B	15-04-1997
		AU 6984594 A	17-01-1995
		EP 0737071 A	16-10-1996
		JP 2548507 B	30-10-1996
		JP 7099977 A	18-04-1995
		US 5683988 A	04-11-1997
		ZA 9404185 A	08-02-1995

AvK | Sg | W | Da | Hi | HPJ | ME | TW | JH | KB

02. FEB. 2000

K F.10.12.00 /10.12.00

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

MEYERS, Hans-Wilhelm
Postfach 10 22 41
D-50462 Köln
ALLEMAGNE

Date of mailing (day/month/year) 19 January 2000 (19.01.00)	
Applicant's or agent's file reference 991058woMekk	**IMPORTANT NOTIFICATION**
International application No. PCT/EP99/04013	International filing date (day/month/year) 10 June 1999 (10.06.99)
International publication date (day/month/year) 16 December 1999 (16.12.99)	Priority date (day/month/year) 10 June 1998 (10.06.98)
Applicant BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
10 June 1998 (10.06.98)	98110709.7	EP	21 Dece 1999 (21.12.99)
25 July 1998 (25.07.98)	98113974.4	EP	21 Dece 1999 (21.12.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. (41-22) 740.14.35

Authorized officer
G. Bähr
Telephone No. (41-22) 338.83.38

003058722

PATENT COOPERATION TREATY

PCT

09/701583

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
991058woMekk		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/04013	10/06/1999	10/06/1998

Applicant

BIOGNOSTIK GES. FÜR BIOMOLEKULARE DIAGNOSTIK MBH

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/04013

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-9,12-13 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-9,12-13 (part)

Present Claim 1 relates to a medicament comprising a combination of;

i) an inhibitor of TGF-beta or TGF-beta receptors, VEGF or VEGF receptors, interleukin-10 or interleukin-10 receptors, PGE-2 or PGE-2 receptors and,

ii) a stimulator positively effecting an immune response

Each of these broad functionally defined categories of compounds (i) and (ii) includes many thousands of possible medicaments with the result that present Claim 1 comprises many, possible permutations. Furthermore, the Applicant is advised that, in general, compounds cannot be sufficiently defined by their function to the extent that a full search can be carried out.

Moreover, the definition of the "stimulator positively affecting the immune response" is vague and unclear.

Hence, in view of the above considerations a search of the full breadth of the present Claims 1 to 9 and 12 to 13 is impossible. Consequently, the search has been directed, in so far as practically feasible, to the general idea underlying the present invention and those combinations of medicaments which are most clearly described and exemplified namely combinations of;

i) an antisense oligonucleotide directed against TGF-beta or TGF-beta receptors, VEGF or VEGF receptors, interleukin-10 or interleukin receptors, PGE-2 or PGE-2 receptors, particularly the oligonucleotides of Claim 10 and;

ii) a stimulator selected from GM-CSF, SCF, CSF, IFN-gamma, FLT-3, MCP-1, IL-2, IL-4, IL-12, IL-18 (see page 3 lines 3 to 6); the stimulators described in categories (a), (b), (c) on present page 3; ras protein, p53 protein, EGF-receptor protein, retinoblastoma protein and derivatives thereof (see category (l) on present page 4).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 to 9, 12 and 13

Medicament comprising

i) an inhibitor of TGF-beta or TGF-beta receptors, VEGF or VEGF receptors, interleukin-10 or interluekin receptors, PGE-2 or PGE-2 receptors in combination with;

ii) a stimulator positively effecting an immune response

2. Claims: 10,11 (part)

An oligonucleotide having the sequence No. 55

3. Claims: 10,11 (part)

An oligonucleotide having the sequence No. 56

Each of the further sequences 57 to 213 relates to a further separate invention. Hence, inventions 4 to 158 are as defined herein above for invention 3. wherein oligonucleotide sequence No. 56 is replaced in turn by each of sequence No.'s 57 to 213.

i.e the present application comprises 160 inventions in total

With reference to the above identified inventions, it is noted that antisense oligonucleotides against TGF-beta at least are known (see each of the documents cited in the accompanying search report). Hence, there is no novel common inventive concept or idea linking the production of further anti-sense oligonucleotides as defined in Claims 10 and 11 which are directed against diverse targets such as TGF-beta, VEGF, flt, flkl and MCP-1.

Since all searchable claims could be searched without excessive additional effort justifying an additional fee, the present search report relates to ALL INVENTIONS IDENTIFIED ABOVE.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JACHIMCZAK P ET AL: "The effect of transforming growth factor-beta 2-specific phosphorothioate-anti-sense oligodeoxynucleotides in reversing cellular immunosuppression in malignant glioma." JOURNAL OF NEUROSURGERY, vol. 78, no. 6, June 1993 (1993-06), pages 944-951, XP000886109 final paragraph of the "Materials and methods" on page 946 "discussion" on page 948 ---	10,11
X	SPEARMAN M ET AL: "Antisense oligodeoxyribonucleotide inhibition of TGF - beta 1 gene expression and alterations in the growth and malignant properties of mouse fibrosarcoma cells." GENE, vol. 149, no. 1, 4 November 1994 (1994-11-04), pages 25-9, XP002089439 abstract; table 1 ---	10,11
X	WO 95 00103 A (CHUNG HUN TAEG ;IL YANG PHARM CO LTD (KR)) 5 January 1995 (1995-01-05) claim 5 ---	10,11
X	AKPORIAYE ET AL: "Concomitant expression of interferon-gamma and antisense TGF-beta transgenes enhances the immunogenicity of a murine mammary carcinoma" CANCER GENE THERAPY vol. 4, no. 6 conf. suppl. S55 6th International Conference on Gene Therapy of Cancer, San Diego, California, USA, Nov 20-22, 1997 XP000886176 abstract -----	1-13

11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/04013

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9602143 A	01-02-1996	US 5772995 A	30-06-1998
		AU 711730 B	21-10-1999
		AU 3217895 A	16-02-1996
		CA 2195334 A	01-02-1996
		EP 0771147 A	07-05-1997
WO 9425588 A	10-11-1994	AU 6794594 A	21-11-1994
		EP 0695354 A	07-02-1996
		JP 8509370 T	08-10-1996
WO 9500103 A	05-01-1995	KR 9705347 B	15-04-1997
		AU 6984594 A	17-01-1995
		EP 0737071 A	16-10-1996
		JP 2548507 B	30-10-1996
		JP 7099977 A	18-04-1995
		US 5683988 A	04-11-1997
		ZA 9404185 A	08-02-1995

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING DOCUMENT TRANSMITTED

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as designated Office

Date of mailing (day/month/year)
19 January 2000 (19.01.00)

International application No.
PCT/EP99/04013

International filing date (day/month/year)
10 June 1999 (10.06.99)

Applicant
BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH et al

The International Bureau transmits herewith the following documents and number thereof:

_____ cop(ies) of priority document(s) (Rule 17.2(a))

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

G. Bähr

Telephone No.: (41-22) 338.83.38

P. ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

MEYERS, Hans-Wilhelm
Postfach 10 22 41
D-50462 Köln
ALLEMAGNE

Date of mailing (day/month/year) 19 January 2000 (19.01.00)	
Applicant's or agent's file reference 991058woMekk	**IMPORTANT NOTIFICATION**
International application No. PCT/EP99/04013	International filing date (day/month/year) 10 June 1999 (10.06.99)
International publication date (day/month/year) 16 December 1999 (16.12.99)	Priority date (day/month/year) 10 June 1998 (10.06.98)
Applicant BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
10 June 1998 (10.06.98)	98110709.7	EP	21 Dece 1999 (21.12.99)
25 July 1998 (25.07.98)	98113974.4	EP	21 Dece 1999 (21.12.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

G. Bähr

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
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in its capacity as elected Office

Date of mailing (day/month/year) 10 February 2000 (10.02.00)	
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International filing date (day/month/year) 10 June 1999 (10.06.99)	**Priority date** (day/month/year) 10 June 1998 (10.06.98)
Applicant SCHLINGENSIEPEN, Karl-Hermann et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 December 1999 (24.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Villet
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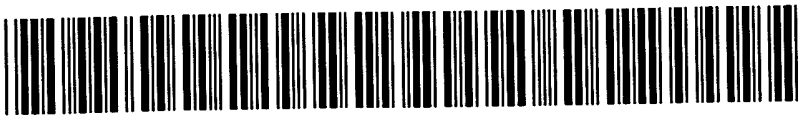

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